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AGENT FOR EXTERNAL USE CONTAINING PLANT EXTRACT
[Shokubutsu chushutsu-butsu o gan'yu suru gaiyozai]

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SPECIFICATIONS /1*

[Title of the Invention]

Agent For External Use Containing Plant Extract

[Claims] /2

[Claim 1] Skin whitening agent containing one or more types of plant extract as active ingredient selected from Artocarpus lakoocha Roxb., Streblus asper Lour., Blumea balsamifera DC., Pluchea indica (L.) Less., Coccinia indica Wight & Arnott, Coccinia grandis Voight, Gloriosa superba L., Heliotropium indicum R. Br., Hibiscus sabdariffa L., Mammea siamensis Kosterm., Michelia champaca L., Murraya paniculata Jack, Mitragyna speciose (Korth.) Havil., Morinda citrifolia L., Randia siamensis Craib., and Solanum trilosatum L.

[Claim 2] Agent for external use, characterized by containing the skin whitening agent described in Claim 1.

[Claim 3] Agent for external use described in Claim 2, characterized by the content of the skin whitening agent being 0.0005 to 5 wt% converted to dry solid parts of plant extract.

[Claim 4] Active oxygen scavenging agent containing one or more types of plant extract as active ingredient selected from Artocarpus lakoocha Roxb., Streblus asper Lour., Blumea balsamifera DC., Pluchea indica (L.) Less., Coccinia indica Wight & Arnott, Coccinia grandis Voight, Gloriosa superba L., Heliotropium indicum R. Br., Hibiscus

*Numbers in the margin indicate pagination in the foreign text.

sabdariffa L., Mammea siamensis Kosterm., Michelia champaca L., Murraya paniculata Jack, Mitragyna speciose (Korth.) Havil, Morinda citrifolia L., Randia siamensis Craib., Solanum trilosatum L., Diospyros mollis Griff., Elephantopus scber L., Mesua ferrea L., Micromelum minutum Seem., Orthosiphon stamineus, and Solanum violaceum Ortega.

[Claim 5] Agent for external use, characterized by containing the active oxygen scavenging agent described in Claim 4.

[Claim 6] Agent for external use described in Claim 4, characterized by the content of the active oxygen scavenging agent being 0.0005 to 5 wt% converted to dry solid parts of plant extract.

[Claim 7] Antimicrobial agent containing one or more types of plant extract as active ingredient selected from Artocarpus lakoocha Roxb., Streblus asper Lour., Blumea balsamifera DC., Pluchea indica (L.) Less., Coccinia indica Wight & Arnott, Coccinia grandis Voight, Gloriosa superba L., Heliotropium indicum R. Br., Hibiscus sabdariffa L., Mammea siamensis Kosterm., Michelia champaca L., Micromelum minutum Seem., Murraya paniculata Jack, Mitragyna speciose (Korth.) Havil., Morinda citrifolia L., Randia siamensis Craib., Orthosiphon stamineus, Solanum trilosatum L., and Solanum violaceum Ortega.

[Claim 8] Agent for external use, characterized by containing the antimicrobial agent described in Claim 7.

[Claim 9] Agent for external use described in Claim 7, characterized by the content of the antimicrobial agent being 0.0005

to 5 wt% converted to dry solid parts of plant extract.

[Detailed Explanation of the Invention]

[Industrial Field of Application]

The present invention pertains to skin whitening agents, active oxygen scavenging agents, antimicrobial agents, and agents for external use containing these having extracts from specific plants as active ingredients. More particularly, the present invention pertains to (1) skin whitening agents with excellent skin whitening effect and useful for inhibiting production of melanin and preventing and improving conditions resulting from sun exposure, such as pigment deposits, spots, or freckles; (2) active oxygen scavenging agents with excellent effects such as skin antiaging effect or skin roughness improving effect, and capable of preventing production of peroxide lipids caused by generation of active oxygen on skin surfaces and in skin, and skin conditions such as inflammation, darkening, or aging; (3) antimicrobial agents showing high antimicrobial activity and high safety, with excellent preservative effect, and capable of inhibiting proliferation of bacteria in products; and agents for external use containing these.

[Prior Art]

In prior art, skin agents for external use such as emulsions, creams, toilet waters, packs, cleaners, foundations, dispersions, or ointments have contained skin whitening agents such as calamine, /3
ascorbic acids, glutathione, colloidal sulfur, hydroquinone, or

placental extracts to prevent conditions such as spots or freckles caused by darkening of skin and pigment deposits resulting from sun exposure or the like. Often, however, these skin whitening agents do not obtain the desired pharmaceutical effect due to inadequate skin whitening effect or deterioration in the formulation, and it would be desirable to offer compounds having more excellent properties.

Active oxygen scavenging agents such as superoxide dismutase or mannitol are also added to the above-mentioned skin whitening agents for the purpose of preventing both production of peroxide lipids and skin inflammation, darkening, or aging. In recent years, the negative effects of active oxygen on the body have been seen as one of the causes of skin aging. Known types of active oxygen include singlet oxygen, hydroxy radicals, hydrogen peroxide, and superoxides. These are known to damage lipids, nucleic acids, proteins, and enzymes. Accumulated damage by these types of active oxygen causes reduction in body functions and is one of the sources of aging. Excessive damage by these can also lead to illness or death. Therefore, various active oxygen scavenging agents have been developed in prior art to prevent damage by these. There is a demand for development of highly effective active oxygen scavenging agents for the purposes of protecting the body and preventing aging. Given that they are to be applied to the body, however, these must be fully satisfactory from the standpoint not only of these effects, but also safety. Therefore, there is a demand for development of novel pharmaceutical ingredients

that have excellent safety on the skin as well as excellent active oxygen scavenging effect, and are ideal when applied to the body.

Furthermore, in prior art, agents for external use such as emulsions, creams, toilet waters, packs, cleaners, foundations, lipsticks, shampoo rinses, or conditioners have contained various antimicrobial agents such as paraoxybenzoate derivatives, benzalkonium chloride, triclosan, isopropyl methyl phenol, Morus bombycis extract, Glycyrrhiza glabra extract, or aloe extract for purposes such as preserving products or inhibiting proliferation of bacteria that cause acne or dandruff. These antimicrobial agents, however, sometimes have problems in terms of safety and their content in agents for external use must be restricted, and while agents such as plant extracts do not have problems in terms of safety, many have little antimicrobial effect. Therefore, there is a demand for development of antimicrobial pharmaceutical ingredients that have both high effect and high safety.

[Problems that the Invention is to Solve]

Therefore, the purpose of the present invention is to offer novel pharmaceutical ingredients that lack the drawbacks of prior art compounds having comparable effect as skin whitening agents, active oxygen scavenging agents, or antimicrobial agents, and agents for external use containing these.

[Means of Solving the Problems]

As a result of broad study of the pharmacological action of various naturally present substances to solve the problems described above, the present inventors discovered that extracts from specific plants had a high melanin production inhibiting effect, active oxygen scavenging effect, and/or antimicrobial effect, and so perfected the present invention.

Specifically, the present invention offers a skin whitening agent, and an agent for external use containing this, that has one or more types of plant extract as active ingredient selected from Artocarpus lakoocha Roxb., Streblus asper Lour., Blumea balsamifera DC., Pluchea indica (L.) Less., Coccinia indica Wight & Arnott, Coccinia grandis Voight, Gloriosa superba L., Heliotropium indicum R. Br., Hibiscus sabdariffa L., Mammea siamensis Kosterm., Michelia champaca L., Murraya paniculata Jack, Mitragyna speciose (Korth.) Havil., Morinda citrifolia L., Randia siamensis Craib., and Solanum trilosatum L.

The present invention also offers an active oxygen scavenging agent, and an agent for external use containing this, that has one or more types of plant extract as active ingredient selected from Artocarpus lakoocha Roxb., Streblus asper Lour., Blumea balsamifera DC., Pluchea indica (L.) Less., Coccinia indica Wight & Arnott, Coccinia grandis Voight, Gloriosa superba L., Heliotropium indicum R. Br., Hibiscus sabdariffa L., Mammea siamensis Kosterm., Michelia

champaca L., Murraya paniculata Jack, Mitragyna speciose (Korth.) Havil., Morinda citrifolia L., Randia siamensis Craib., Solanum trilosatum L., Diospyros mollis Griff., Elephantopus scber L., Mesua ferrea L., Micromelum minutum Seem., Orthosiphon stamineus, and Solanum violaceum Ortega.

Furthermore, the present invention offers an antimicrobial agent, and an agent for external use containing this, that has one or more types of plant extract as active ingredient selected from Artocarpus lakoocha Roxb., Streblus asper Lour., Blumea balsamifera DC., Pluchea indica (L.) Less., Coccinia indica Wight & Arnott, Coccinia grandis Voight, Gloriosa superba L., Heliotropium indicum R. Br., Hibiscus sabdariffa L., Mammea siamensis Kosterm., Michelia champaca L., Micromelum minutum Seem., Murraya paniculata Jack, Mitragyna speciose (Korth.) Havil., Morinda citrifolia L., Randia siamensis Craib., Orthosiphon stamineus, Solanum trilosatum L., and Solanum violaceum Ortega. /4

[Mode for Reducing the Invention to Practice]

All of the plants used in the present invention are plants found in the Southeast Asia region, such as Thailand or Indonesia. Specific plants are listed below:

(1) Moraceae Artocarpus lakoocha Roxb.

(2) Moraceae Streblus asper Lour.

(3) Compositae Blumea balsamifera DC.

(4) Compositae Pluchea indica (L.) Less.

(5) Cucurbitaceae Coccinia indica Wight & Arnott

(6) Cucurbitaceae Coccinia grandis Voight

(7) Liliaceae Gloriosa superba L.

(8) Boraginaceae Heliotropium indicum R. Br.

(9) Malvaceae Hibiscus sabdariffa L.

(10) Guttiferae Mammea siamensis Kosterm.

(11) Magnoliaceae Michelia champaca L.

(12) Rutaceae Murraya paniculata Jack

(13) Rubiaceae Mitragyna speciose (Korth.) Havil.

(14) Rubiaceae Morinda citrifolia L.

(15) Rubiaceae Randia siamensis Craib.

(16) Solanaceae Solanum trilosatum L.

(17) Ebenaceae Diospyros mollis Griff.

(18) Compositae Elephantopus scber L.

(19) Guttiferae Mesua ferrea L.

(20) Rutaceae Micromelum minutum Seem.

(21) Labiatae Orthosiphon stamineus

(22) Solanaceae Solanum violaceum Ortega

The plant extracts used as active ingredients in the present invention are prepared by extracting using a suitable extraction solvent from the leaves or branches or from the stem, bark, flowers, seeds, or roots of the above-mentioned plants, either fresh or dried. The extraction method for this is not specially limited, but an example is the method of extracting at a low temperature or from room

temperature to a heated temperature using various suitable solvents.

One or more solvents can be used for the extraction solvent. These include lower monovalent alcohols such as methyl alcohol or ethyl alcohol, or liquid polyvalent alcohols such as glycerin, propylene glycol, or 1,3-butylene glycol. An example of a preferred extraction method is the method of extracting for one to five days at room temperature using ethyl alcohol or 1,3-butylene glycol of 0% to 80% (v/v) moisture concentration, then filtering, allowing the resulting filtrate to sit for one week to mature, and filtering again.

The skin whitening agent of the present invention is prepared by using an extract obtained as described above for plants (1) to (16) listed above as is or by combining with a suitable cosmetic or drug carrier after refining or diluting as required.

The active oxygen scavenging agent of the present invention is prepared by using an extract obtained as described above for plants (1) to (22) listed above as is or by combining with a suitable cosmetic or drug carrier after refining or diluting as required.

Furthermore, the antimicrobial agent of the present invention is prepared by using an extract obtained as described above for plants (1) to (22) listed above as is or by combining with a suitable cosmetic or drug carrier after refining or diluting as required.

There is no special limitation on the mode when distributing the skin whitening agent of the present invention obtained as described

above in an agent for external use, and a suitable amount can be distributed in any suitable formulation that is easy to apply externally. Examples of formulations that are easy to apply externally are skin agents for external use, including skin care cosmetics such as emulsions, creams, toilet waters, packs, or cleaners, makeup cosmetics, and pharmaceuticals for external use such as dispersions or ointments.

There also is no special limitation on the mode when distributing the active oxygen scavenging agent of the present invention in an agent for external use, and a suitable amount can be distributed in any suitable formulation that is easy to apply externally. Examples of formulations that are easy to apply externally are skin agents for external use, including skin care cosmetics such as emulsions, creams, toilet waters, packs, cleaners, makeup cosmetics, dispersions, or ointments, and pharmaceuticals for external use. /5

Furthermore, there is no special limitation on the mode when distributing the antimicrobial agent of the present invention in an agent for external use, and a suitable amount can be distributed in any suitable formulation that is easy to apply externally. Examples of formulations that are easy to apply externally are agents for external use, including toiletry products such as disinfectants, deodorizers, antiperspirants, bath products, toothpastes, or mouthwashes, skin care cosmetics such as emulsions, creams, toilet

waters, packs, or cleaners, makeup cosmetics such as foundations, grounds, eye shadows, or lipsticks, hair cosmetics such as hair growth products, hair tonics, shampoos, rinses, or conditioners, and other medical and makeup products for external use.

Depending on the mode, the agent for external use of the present invention can contain ingredients used in agents for external use, such as standard cosmetics or pharmaceuticals for external use, other than the chemicals listed above within a range that does not damage the effects of the present invention; for example, fragrances, and beauty aid ingredients such as bactericides, purified water, lower alcohols, polyvalent alcohols, oily ingredients, powders, surface active agents, thickeners, coloring matter, preservatives, moisturizers, antioxidants, antiphlogistics, ultraviolet absorbers, vitamins, amino acids, astringents, cell excipients, skin whitening agents, percutaneous absorption promoters, other plant extracts, or animal extracts.

The content of each of the chemicals described above in the agent for external use of the present invention is preferably 0.0005 to 5 wt% (hereafter indicated simply as "%"), and more preferably 0.002 to 2%, converted to dry solid parts of plant extract. The plant extract that is the active ingredient of each chemical can be distributed consistently within this range, and a high skin whitening effect, active oxygen scavenging effect, or antimicrobial effect can be achieved. When using an extract, moreover, the concentration of

this extract is not limited in any way so long as the content of dry solid parts comprising the solute is within this range.

[Working Examples]

Next, the present invention will be explained in greater detail by citing reference examples, test examples, and working examples, but the present invention is not in any way limited to these examples.

Working Example 1

Production of Plant Extract (Skin Whitening Agent): 100 mL Ethyl alcohol of 50% (v/v) moisture concentration were added to 10 g of each plant, dry, listed in Table 1 and extracted for three days at room temperature, then filtered to give each plant extract. This was taken as the skin whitening agent of the present invention. The dry solid parts of these extracts and the results of the tyrosinase activity inhibition test described below are also given in Table 1.

[Table 1]

Skin Whitening Agent		Dry Solid Parts (%)	Tyrosinase Activity Inhibition Rate (%) Amount Added in Test (mL)		
			0.01	0.05	0.1
Invention Product	Artocarpus lakoocha Roxb. extract *1	4.1	30.3	77.4	94.5
	Streblus asper Lour. extract *1	1.2	45.1	88.0	97.5
	Blumea balsamifera DC. extract *1	2.0	23.4	50.9	80.3
	Pluchea indica (L.) Less. extract *1	3.4	42.1	77.7	92.6
	Coccinia indica Wight & Arnott extract *1	1.8	15.2	50.8	86.3
	Coccinia grandis Voight extract *1	1.8	17.7	45.5	90.9
	Gloriosa superba L. extract *1	2.2	42.0	76.2	95.4
	Heliotropium indicum R. Br. extract *1	2.7	39.4	68.3	89.2
	Hibiscus sabdariffa L. extract *1	3.7	29.0	54.4	84.0
	Mammea siamensis Kosterm. extract *1	2.3	34.9	60.6	91.7
	Michelia champaca L. extract *1	3.3	25.8	56.1	85.1
	Murraya paniculata Jack extract *1	2.8	27.4	44.7	81.9
	Mitragyna speciose (Korth.) Havil. extract *1	2.3	43.8	75.3	98.5
	Morinda citrifolia L. extract *1	4.8	19.2	53.6	82.2
	Randia siamensis Craib. extract *1	2.1	33.3	58.0	85.7
	Solanum trilosatum L. extract *1	2.9	27.9	57.1	92.8
Comparison Product	Morus bombycis extract *2	1.8	15.1	38.8	56.5

*1 Produced in Working Example 1
*2 Produced in Reference Example 1

Reference Example 1

Production of Morus bombycis Extract and Sophora angustifolia Extract: 100 mL Ethyl alcohol of 50% (v/v) moisture concentration were added to 10 g each of Morus bombycis (Pharmacopoeia Japonica) and Sophora angustifolia (Pharmacopoeia Japonica) and extracted for three days at room temperature, then filtered to give Morus bombycis extract and Sophora angustifolia extract. The dry solid parts at this time were 1.8% Morus bombycis extract and 2.8% Sophora angustifolia

extract.

Test Example 1

Tyrosine Activity Inhibition Test: The tyrosine activity inhibition rate was investigated by the following method for each of the skin whitening agents of the present invention obtained in Working Example 1. The tyrosine activity inhibition rate of the Morus bombycis extract of Reference Example 1, which is known to have an inhibitory effect on tyrosine activity, was investigated as a comparison example.

Tyrosine activity was measured as follows: First, 0.1 mL enzyme solution (produced by Sigma Corporation, 10 mg of 28,000 units tyrosine dissolved in 20 mL 0.1 M phosphoric acid buffer (pH 6.8)) was added to each sample, more 0.1 M phosphoric acid buffer (pH 6.8) was added to bring to 4.0 mL, and this system was incubated for ten minutes at 25°C. Next, a substrate solution (198.0 mg L-DOPA /6 (produced by Tokyo Kasei KK) dissolved in 100 mL 0.1 M phosphoric acid buffer (pH 6.8)) already kept at 25°C was added and reacted for ten minutes.

After reacting, absorptance at 475 nm (OD_S) was measured. Absorptance when reacted using the above-mentioned enzyme after heating and deactivating (OD_{HE}) and absorptance when no sample was added (OD_B) were measured in the same way. The inhibition rate of tyrosine activity was calculated by the following formula. The result is given in Table 1.

[Numerical Expression 1]

$$\text{tyrosine activity inhibition rate (\%)} = \frac{OD_B - (OD_S - OD_{HE})}{OD_B} \times 100$$

OD_S: absorptance when sample was added

OD_B: absorptance when no sample was added

OD_{HE}: absorptance after enzyme was heated and deactivated

Result: As is clear from the results shown in Table 1 above, the skin whitening agents of the present invention showed an extremely high inhibitory effect on tyrosine activity compared to the conventional Morus bombycis extract.

Test Example 2

Melanin Production Inhibition Test by Cell Culture: Mouse-derived B16 melanoma culture cells were used. A suitable amount of culture medium was placed in two six-well Petri dishes, then B16 melanoma cells were inoculated and left in a 5% carbon dioxide concentration at 37°C. The next day, specimen solutions prepared so as to contain 0 (control), 1, 10, and 100 μg/mL of each of the skin whitening agents of the present invention obtained in Working Example 1 were added and stirred in. On the fifth day of culture, the culture medium was replaced and the specimen solutions were added again. The next day, the culture medium was removed and the cells in one Petri dish were washed in a phosphoric acid buffer, then collected. The degree of whitening of B16 melanoma culture cells was evaluated by the following criteria. The same test was also conducted for the Sophora

angustifolia extract of Reference Example 1, which is known to have an inhibitory effect on melanin production.

Evaluation Criteria

++: much whiter than the control

+: clearly whiter than the control

±: somewhat whiter than the control

-: just as black as the control

For the other Petrie dish, the cells were fixed in formalin, then added to a 1% crystal violet solution and stained. The number of surviving cells (A) and the number of control cells (B) were measured by a monocell reader from the absorptance of 550 nm for each specimen concentration. The cell survival rate was calculated by the following formula. The above results are shown in Table 2.

[Numerical Expression 2]

$$\text{cell survival rate (\%)} = \frac{A}{B} \times 100$$

Results

[Table 2] /7

Sample		Specimen Solution Concentration (μg/mL)	1	10	100
Invention Skin Whitening Agent	Artocarpus lakoocha Roxb. extract *1	skin whitening agent	±	+	++
		cell survival rate (%)	92	90	78
	Streblus asper Lour. extract *1	skin whitening agent	±	±	+
		cell survival rate (%)	106	107	103
	Blumea balsamifera DC. extract *1	skin whitening agent	-	+	++
		cell survival rate (%)	115	122	104
	Pluchea indica (L.) Less. extract *1	skin whitening agent	-	+	+
		cell survival rate (%)	96	99	103
	Coccinia indica Wight & Arnott extract *1	skin whitening agent	+	++	++
		cell survival rate (%)	89	105	105
	Coccinia grandis Voight extract *1	skin whitening agent	+	++	++
		cell survival rate (%)	93	114	118
	Gloriosa superba L. extract *1	skin whitening agent	-	±	+
		cell survival rate (%)	100	102	83
	Heliotropium indicum R. Br. extract *1	skin whitening agent	±	±	++
		cell survival rate (%)	100	101	86
	Hibiscus sabdariffa L. extract *1	skin whitening agent	-	±	+
		cell survival rate (%)	96	94	99
	Mammea siamensis Kosterm. extract *1	skin whitening agent	±	+	++
		cell survival rate (%)	86	84	89
	Michelia champaca L. extract *1	skin whitening agent	-	+	+
		cell survival rate (%)	100	104	103
	Murraya paniculata Jack extract *1	skin whitening agent	-	±	++
		cell survival rate (%)	98	99	96
	Mitragyna speciose (Korth.)Havil. extract *1	skin whitening agent	-	±	+
		cell survival rate (%)	98	93	102
	Morinda citrifolia L. extract *1	skin whitening agent	±	±	±
		cell survival rate (%)	100	95	80
	Randia siamensis Craib. extract *1	skin whitening agent	±	+	+
		cell survival rate (%)	91	104	106
	Solanum trilosatum L. extract *1	skin whitening agent	-	+	+
		cell survival rate (%)	115	107	97
Comparison Skin Whitening Agent	Morus bombycis extract *2	skin whitening agent	-	-	+
		cell survival rate (%)	98	67	51

*1 Produced in Working Example 1
*2 Produced in Reference Example 1

As is clear from the results in Table 2, the skin whitening agents of the present invention were found to have extremely high

melanin production inhibitory capacity and low toxicity to B16 melanoma culture cells compared to the conventional Sophora angustifolia extract. Therefore, the skin whitening agents of the present invention were found to achieve an extremely excellent melanin production inhibitory effect when applied to the skin, and effectively inhibited conditions such as spots or freckles resulting from sun exposure.

Working Example 2

Cream: Creams with the compositions shown in Table 3 were prepared by the method given below and investigated for their skin whitening effect. The results are given in Table 4.

Composition

[Table 3]

Composition (%)	Invention Products	Comparison Products		
	1 to 16	1	2	3
(1) honey	6.0	6.0	6.0	6.0
(2) hexadecanol	5.0	5.0	5.0	5.0
(3) reduced lanolin	5.0	5.0	5.0	5.0
(4) squalane	30.0	30.0	30.0	30.0
(5) lipophilic glyceryl monostearate	4.0	4.0	4.0	4.0
(6) polyoxyethylene sorbitan monolaurate (20E.O)	2.0	2.0	2.0	2.0
(7) skin whitening agent of the present invention *1	5.0	5.0	—	—
(8) Morus bombycis extract *2	—	—	5.0	—
(9) phosphate-L-ascorbyl magnesium *3	—	—	—	—
(10) preservative	suitable amount	suitable amount	suitable amount	suitable amount
(11) fragrance	suitable amount	suitable amount	suitable amount	suitable amount
(12) purified water	suitable amount	suitable amount	suitable amount	suitable amount

*1 Produced in Working Example 1
*2 Produced in Reference Example 1
*3 Produced by Nikko Chemicals Co., Ltd.

Production /8

A. Ingredients (1) to (6) and (10) are combined, heated, and kept at 70°C.

B. Ingredients (9) and (12) are combined, heated, and kept at 70°C.

C. B is added to A, combined, then cooled.

D. Ingredients (7), (8), and (11) are added to C to give a cream.

Test Method

A panel of ten women ages 28 to 55 was enlisted to test one cream product. They applied a suitable amount of the test cream after

washing their faces twice daily, every morning and every evening, for a period of twelve weeks. The whitening effect of applying the cream was evaluated by the following criteria.

Evaluation Criteria

<Evaluation>	<Definition>
effective	skin darkness not noticeable
somewhat effective	skin darkness not very noticeable
ineffective	no change from before use

Results

[Table 4]

Cream	Skin Whitening Agent	Skin Whitening Effect		
		effective	somewhat effective	ineffective
Invention Product 1	Artocarpus lakoocha Roxb. extract *1	9	1	0
Invention Product 2	Streblus asper Lour. extract *1	8	2	0
Invention Product 3	Blumea balsamifera DC. extract *1	9	1	0
Invention Product 4	Pluchea indica (L.) Less. extract *1	7	2	1
Invention Product 5	Coccinia indica W. & A. extract *1	9	0	1
Invention Product 6	Coccinia grandis Voight extract *1	10	0	0
Invention Product 7	Gloriosa superba L. extract *1	7	2	1
Invention Product 8	Heliotropium indicum R. Br. extract *1	8	1	1
Invention Product 9	Hibiscus sabdariffa L. extract *1	6	2	2
Invention Product 10	Mammea siamensis Kosterm. extract *1	8	1	1
Invention Product 11	Michelia champaca L. extract *1	6	3	1
Invention Product 12	Murraya paniculata Jack extract *1	8	2	0
Invention Product 13	Mitragyna speciose (K.) H. extract *1	6	2	2
Invention Product 14	Morinda citrifolia L. extract *1	5	3	2
Invention Product 15	Randia siamensis Craib. extract *1	7	1	2
Invention Product 16	Solanum trilosatum L. extract *1	7	3	0
Comparison Product 1	Morus bombycis extract *2	2	3	5
Comparison Product 2	phosphate-L-ascorbyl magnesium *3	3	3	4
Comparison Product 3	no skin whitening agent	0	2	8

*1 Produced in Working Example 1
*2 Produced in Reference Example 1
*3 Produced by Nikko Chemicals Co., Ltd.

As shown by the results in Table 4, all of the products of the present invention could clearly prevent and improve conditions such as skin "darkness" and produce beautiful skin by application to the skin.

Working Example 3

Toilet Water: A toilet water was prepared by the following formula using the production method described below.

Formula	(%)
(1) glycerin	5.0
(2) 1,3-butylene glycol	6.5
(3) polyoxyethylene (20E.O) sorbitan monolaurate	1.2
(4) ethyl alcohol	5.0
(5) Streblus asper extract *1	40.0
(6) preservative	suitable amount
(7) fragrance	suitable amount
(8) purified water	balance

*1 Produced in Working Example 1

Production

A. Ingredients (3), (4), (6), and (7) are combined and dissolved.

B. Ingredients (1), (2), (5), and (8) are combined and dissolved.

C. A and B are evenly combined to give a toilet water.

Working Example 4

Emulsion: An emulsion was prepared by the following formula using the production method described below. /9

Formula	(%)
(1) polyoxyethylene (10E.O) sorbitan monolaurate	1.0
(2) polyoxyethylene (60E.O) sorbitan monolaurate	0.5
(3) glyceryl monostearate	1.0
(4) stearic acid	0.5
(5) behenyl alcohol	0.5
(6) squalane	8.0
(7) Vitamin E acetate	0.2

(8)	preservative	suitable amount
(9)	Coccinia grandis Voight extract *1	0.1
(10)	Mammea siamensis Kosterm. extract *1	0.1
(11)	Solanum trilosatum L. extract *1	0.1
(12)	oxybenzone	0.1
(13)	phosphate-L-ascorbyl magnesium	0.1
(14)	carboxyvinyl polymer	0.1
(15)	sodium hydroxide	0.05
(16)	ethyl alcohol	5.0
(17)	purified water	balance
(18)	fragrance	suitable amount

*1 Produced in Working Example 1

Production

A. Ingredients (13) to (17) are heated to combine and kept at 70°C.

B. Ingredients (1) to (8) are heated to combine and kept at 70°C.

C. A is added to B and evenly emulsified.

D. C is cooled, then ingredients (9) to (11) and (18) are added and evenly combined to give an emulsion.

Working Example 5

Cream: A cream was prepared by the following formula using the production method described below.

Formula		(%)
(1)	polyoxyethylene (40E.O) sorbitan monolaurate	2.0
(2)	glycerin monostearate (self-emulsifying)	5.0
(3)	stearic acid	5.0
(4)	behenyl alcohol	0.5
(5)	squalane	15.0
(6)	cetyl isooctoate	5.0
(7)	octyl paramethoxycinnamate	5.0
(8)	preservative	suitable amount
(9)	1,3-butylene glycol	5.0
(10)	Gloriosa superba L. extract *1	1.0
(11)	Morinda citrifolia L. extract *1	1.0
(12)	purified water	balance
(13)	fragrance	suitable amount

*1 Produced in Working Example 1

Production

A. Ingredients (1) to (8) are heated to 70°C and dissolved.

B. Ingredients (9) and some of (12) are heated to 70°C.

C. B is added to A, then ingredients (10), (11), the rest of (12), and (13) are added while cooling to give a cream.

The toilet water of Working Example 3, the emulsion of Working Example 4, and the cream of Working Example 5 all had excellent stability over time, could prevent conditions such as skin "darkness" and also improve pigment deposits such as spots by repeated application to the skin, and produced beautiful, clear skin.

Working Example 6

Pack: A pack was prepared by the following formula using the /10 production method described below.

Formula	(%)
(1) polyvinyl alcohol	20.0
(2) ethyl alcohol	20.0
(3) glycerin	5.0
(4) kaolin	6.0
(5) Blumea balsamifera DC. extract *1	5.0
(6) preservative	suitable amount
(7) fragrance	suitable amount
(8) purified water	balance

*1 Produced in Working Example 1

Production

A. Ingredients (1), (3), (4), and (8) are combined, heated to 70°C, and agitated.

B. Ingredients (2) and (6) are combined.

C. The above B is added to the previous A and combined, then cooled,

and ingredients (5) and (7) are evenly dispersed to give a pack.

The pack of Working Example 6 had excellent stability over time, could prevent skin "darkness" and also improve pigment deposits such as spots by repeated application to the skin, and produced beautiful, clear skin.

Working Example 7

Liquid Foundation: A liquid foundation was prepared by the following formula using the production method described below.

Formula		(%)
(1)	lanolin	7.0
(2)	fluid paraffin	5.0
(3)	stearic acid	2.0
(4)	hexadecanol	1.0
(5)	glycerin	5.0
(6)	triethanolamine	1.0
(7)	carboxymethylcellulose	0.7
(8)	purified water	balance
(9)	mica	15.0
(10)	talc	6.0
(11)	coloring pigment	6.0
(12)	Morinda citrifolia L. extract *1	0.5
(13)	Coccinia indica W. & A. extract *1	1.0
(14)	Coccinia grandis Voight extract *1	1.0
(15)	fragrance	suitable amount

*1 Produced in Working Example 1

Production

A. Ingredients (1) to (4) are combined and dissolved.

B. Ingredients (9) to (11) are added to A and evenly combined.

C. Ingredients (5) to (8) are evenly dissolved and kept at 70°C.

D. C is added to B and evenly emulsified.

E. D is cooled, then ingredients (12) to (15) are added to give a liquid foundation.

The liquid foundation of Working Example 7 had excellent stability over time, and by application to the skin, could prevent skin darkening and spots resulting from sun exposure or the like.

Working Example 8

Gel Ointment: A gel ointment was prepared by the following formula using the production method described below.

Formula		(%)
(1)	carboxyvinyl polymer	1.0
(2)	triethanolamine	1.0
(3)	ethyl alcohol	20.0
(4)	Heliotropium indicum R. Br. extract *1	10.0
(5)	purified water	balance

*1 Produced in Working Example 1

Production /11

A. Ingredients (1) and (3) to (5) are combined and dissolved.

B. Ingredient (2) is added to A and evenly combined to give a gel ointment.

The gel ointment of Working Example 8 had excellent stability over time, could regularize skin texture, prevent skin “darkness,” and also improve pigment deposits such as spots by application to the skin, and produced beautiful, clear skin.

Working Example 9

Production of Plant Extract (Active Oxygen Scavenging Agent): 100 mL Ethyl alcohol of 50% (v/v) moisture concentration were added to 10 g of each plant, dry, listed in Table 5 and extracted for three days at room temperature, then filtered to give each plant extract. This was taken as the active oxygen scavenging agent of the present invention.

The dry solid parts of these extracts and results of the superoxide scavenging effect measurement test described below are also given in Table 5.

[Table 5]

Active Oxygen Scavenging Agent		Dry Solid Parts (%)	Superoxide Scavenging Rate (%) Test Dilution Rate (%)		
			0.5	1	0.1
Invention Product	Artocarpus lakoocha Roxb. extract *1	4.1	31.2	79.0	94.3
	Streblus asper Lour. extract *1	1.2	46.0	87.9	95.6
	Blumea balsamifera DC. extract *1	2.0	25.1	50.3	81.3
	Pluchea indica (L.) Less. extract *1	3.4	40.2	78.0	91.3
	Coccinia indica Wight & Arnott extract *1	1.8	16.2	51.2	88.2
	Coccinia grandis Voight extract *1	1.8	17.4	46.3	90.2
	Gloriosa superba L. extract *1	2.2	42.0	78.0	94.6
	Heliotropium indicum R. Br. extract *1	2.7	39.3	67.9	89.6
	Hibiscus sabdariffa L. extract *1	3.7	29.2	53.2	83.4
	Mammea siamensis Kosterm. extract *1	2.3	34.5	61.2	90.6
	Michelia champaca L. extract *1	3.3	25.4	57.0	85.3
	Murraya paniculata Jack extract *1	2.8	27.1	45.1	81.3
	Mitragyna speciose (Korth.) Havil. extract *1	2.3	41.0	74.3	97.7
	Morinda citrifolia L. extract *1	4.8	19.0	52.9	84.1
	Randia siamensis Craib. extract *1	2.1	33.2	57.1	83.6
	Solanum trilosatum L. extract *1	2.9	24.6	56.8	93.0
	Diospyros mollis Griff. extract *1	1.6	30.9	48.5	82.2
	Elephantopus scber L. extract *1	0.2	35.9	57.3	90.5
	Mesua ferrea L. extract *1	0.2	28.6	51.0	85.3
	Micromelum minutum Seem. extract *1	1.4	42.8	63.3	82.4
	Orthosiphon stamineus extract *1	0.8	33.8	62.1	87.0
	Solanum violaceum Ortega extract *1	1.2	31.0	46.5	89.8
Comparison Product	Scutellaria baicalensis extract *2	1.4	21.8	40.9	75.0

*1 Produced in Working Example 1
*2 Produced by Ichimaru Pharcos Co., Ltd.

Test Example 3

Superoxide Scavenging Effect Measurement Test: Superoxide scavenging

activity was measured by the following measurement method using the active oxygen scavenging agents listed in Table 5 as samples.

Measurement Method: A substrate solution of 0.1 mL 3.0 mM xanthine (dissolved in 0.05 M sodium carbonate buffer), 0.1 mL 3.0 mM EDTA, 0.1 mL 0.15% (w/v) bovine serum albumin, and 0.1 mL nitroblue tetrazolium together with 0.1 mL of each test sample diluted in purified water were combined with 2.4 mL 0.05 M sodium carbonate buffer (pH 10.2) and left at 25°C for ten minutes.

Next, 0.1 mL xanthinoxidase solution (diluted by purified water to about 0.04 units/mL), which is an enzyme solution, was added and a reaction was started. After incubating for twenty minutes at 25°C, 0.1 mL 6 mM $CaCl_2$ was added to stop the reaction, then the absorptance of the sample with 0.1 mL xanthinoxidase added was measured. The superoxide scavenging rate was calculated by the following formula. This result is also shown in Table 5.

[Numerical Expression 3]

$$\text{superoxide scavenging rate (\%)} = \frac{B - (A - C)}{B} \times 100$$

A: absorptance of sample when reacted with enzyme

B: absorptance of control when reacted with enzyme

C: absorptance of sample when not reacted with enzyme /12

Result: As is clear from the results shown in Table 5 above, the active oxygen scavenging agents of the present invention showed high superoxide scavenging effect.

Test Example 4

Singlet Oxygen Scavenging Effect Measurement Test: Singlet oxygen scavenging capacity was measured for the active oxygen scavenging agents of the present invention shown in Table 6 using a singlet oxygen measuring instrument developed by the present applicant (see Japan Patent Application No. 5-340377). Rose bengal, which is known to generate singlet oxygen, was used for the singlet oxygen source. Singlet oxygen scavenging capacity was measured after adding test samples.

Measurement Method: 10 μm Rose bengal (50% ethanol solution) was circulated in a flow cell at a speed of 20 mL/min, then this cell was exposed to 200 mW of 514.5 nm argon laser light. Absorptance of 1268 nm light (I_0) was measured when the singlet oxygen excited from the rose bengal returned to its base state

Next, a 50% ethanol solution combining rose bengal and 5% test sample was exposed to the same laser, and absorptance of 1268 nm light (I_S) was measured. The singlet oxygen scavenging rate was calculated by the following formula. The result is given in Table 6.

[Numerical Expression 4]

$$\text{singlet oxygen scavenging rate (\%)} = \frac{I_0 - I_S}{I_S} \times 100$$

Results

[Table 6]

Name of Sample		Singlet Oxygen Scavenging Rate (%)
Invention Active Oxygen Scavenging Agent	Artocarpus lakoocha Roxb. extract *1	85.2
	Streblus asper Lour. extract *1	43.8
	Blumea balsamifera DC. extract *1	52.8
	Pluchea indica (L.) Less. extract *1	61.1
	Coccinia indica Wight&Arnott extract *1	47.9
	Coccinia grandis Voight extract *1	44.0
	Gloriosa superba L. extract *1	39.2
	Heliotropium indicum R. Br. extract *1	55.8
	Hibiscus sabdariffa L. extract *1	83.0
	Mammea siamensis Kosterm. extract *1	77.3
	Michelia champaca L. extract *1	31.5
	Murraya paniculata Jack extract *1	41.3
	Mitragyna speciose (Korth.) Havil. extract *1	66.8
	Morinda citrifolia L. extract *1	36.6
	Randia siamensis Craib. extract *1	50.1
	Solanum trilosatum L. extract *1	47.8
	Diospyros mollis Griff. extract *1	37.2
	Elephantopus scber L. extract *1	30.0
	Mesua ferrea L. extract *1	42.1
	Micromelum minutum Seem. extract *1	32.3
	Orthosiphon stamineus extract *1	38.4
	Solanum violaceum Ortega extract *1	55.0
Comparison Product	Scutellaria baicalensis extract *2	29.8

*1 Produced in Working Example 1
*2 Produced by Ichimaru Pharcos Co., Ltd.

As is clear from the results in Table 6, the active oxygen scavenging agents of the present invention showed high singlet oxygen scavenging capacity.

Working Example 10

Cream: Creams with the compositions shown in Table 3 were prepared by the method given below and investigated for their skin beautifying effect and antiaging effect. The results are given in

Table 8.

Composition

[Table 7] /13

Composition (%)	Invention Products	Comparison Products	
	1 to 22	1	2
(1) honey	6.0	6.0	6.0
(2) hexadecanol	5.0	5.0	5.0
(3) reduced lanolin	5.0	5.0	5.0
(4) squalane	30.0	30.0	30.0
(5) lipophilic glyceryl monostearate	4.0	4.0	4.0
(6) polyoxyethylene sorbitan monolaurate (20E.O)	2.0	2.0	2.0
(7) active oxygen scavenging agent of the present invention *1	5.0	—	—
(8) Scutellaria baicalensis extract *2	—	5.0	—
(9) preservative	suitable amount	suitable amount	suitable amount
(10) fragrance	suitable amount	suitable amount	suitable amount

*1 Produced in Working Example 9
*2 Produced by Ichimaru Pharcos Co., Ltd.

Production

A. Ingredients (1) to (6) and (9) are combined, heated, and kept at 70°C.

B. Ingredient (11) is heated and kept at 70°C.

C. B is added to A, combined, then cooled.

D. Ingredients (7), (8), and (10) are added to C to give a cream.

Test Method

A panel of fifteen women ages 28 to 55 was enlisted to test one cream product. They applied a suitable amount of the test cream after washing their faces twice daily, every morning and every evening, for a period of twelve weeks. The skin beautifying and antiaging effects

of applying the cream were evaluated by the following criteria.

Evaluation Criteria

Skin Beautifying Effect

<Evaluation>	<Definition>
effective	skin texture not noticeable
somewhat effective	skin texture not very noticeable
ineffective	no change from before use

Antiaging Effect

<Evaluation>	<Definition>
effective	skin tone and luster improved
somewhat effective	skin tone and luster somewhat improved
ineffective	no change from before use

Results

[Table 8]

Cream	Active Oxygen Scavenging Agent	Skin Beautifying Effect			Antiaging Effect		
		effective	somewhat effective	ineffective	effective	somewhat effective	ineffective
Invention Product 1	Artocarpus lakoocha Roxb. extract *1	10	3	2	9	3	3
Invention Product 2	Streblus asper Lour. extract *1	11	2	2	12	2	1
Invention Product 3	Blumea balsamifera DC. extract *1	9	4	2	10	2	2
Invention Product 4	Pluchea indica (L.) Less. extract *1	14	1	0	13	0	2
Invention Product 5	Coccinia indica W. & A. extract *1	11	3	1	11	4	0
Invention Product 6	Coccinia grandis Voight extract *1	11	2	2	11	4	0
Invention Product 7	Gloriosa superba L. extract *1	10	2	3	9	4	2
Invention Product 8	Heliotropium indicum R. Br. extract *1	14	1	0	13	2	0
Invention Product 9	Hibiscus sabdariffa L. extract *1	12	2	1	11	3	1
Invention Product 10	Mammea siamensis Kosterm. extract *1	10	4	1	12	2	1
Invention Product 11	Michelia champaca L. extract *1	9	3	3	10	2	3
Invention Product 12	Murraya paniculata Jack extract *1	8	7	0	9	3	2
Invention Product 13	Mitragyna speciose (K.) H. extract *1	11	2	2	10	3	2
Invention Product 14	Morinda citrifolia L. extract *1	10	3	2	10	3	2
Invention Product 15	Randia siamensis Craib. extract *1	9	3	3	11	3	1
Invention Product 16	Solanum trilosatum L. extract *1	9	4	2	11	4	0
Invention Product 17	Diospyros mollis Griff. extract *1	10	3	2	10	3	2
Invention Product 18	Elephantopus scber L. extract *1	12	0	3	13	2	0
Invention Product 19	Mesua ferrea L. extract *1	11	1	3	13	2	0
Invention Product 20	Micromelum minutum Seem. extract *1	12	2	1	13	2	0
Invention Product 21	Orthosiphon stamineus extract *1	13	0	2	14	1	0
Invention Product 22	Solanum violaceum Ortega extract *1	10	5	0	12	3	0
Comparison Product 1	Scutellaria baicalensis extract *2	4	6	5	5	4	6
Comparison Product 2	phosphate-L-ascorbyl magnesium *3	0	3	12	0	4	11

*1 Produced in Working Example 9
*2 Produced by Ichimaru Pharcos Co., Ltd.

As shown by the results in Table 8, applying the products of the present invention to the skin could clearly prevent and improve conditions such as skin "darkness" and produce beautiful skin, and also improved luster and prevented aging of skin. Moreover, no skin conditions were observed that were problematical in terms of safety, such as itching or rash. /14

Working Example 11

Toilet Water: A toilet water was prepared by the following formula using the production method described below.

	Formula	(%)
(1)	glycerin	5.0
(2)	1,3-butylene glycol	6.5
(3)	polyoxyethylene (20E.O) sorbitan monolaurate	1.2
(4)	ethyl alcohol	5.0
(5)	Streblus asper extract *1	20.0
(6)	Coccinia grandis Voight extract *1	20.0
(7)	preservative	suitable amount
(8)	fragrance	suitable amount
(9)	purified water	balance

*1 Produced in Working Example 9

Production

A. Ingredients (3), (4), (7), and (8) are combined and dissolved.

B. Ingredients (1), (2), (5), (6), and (9) are combined and dissolved.

C. A and B are evenly combined to give a toilet water.

Working Example 12

Emulsion: An emulsion was prepared by the following formula using the production method described below.

	Formula	(%)
(1)	polyoxyethylene (10E.O) sorbitan monolaurate	1.0
(2)	polyoxyethylene (60E.O) sorbitan monolaurate	0.5
(3)	glyceryl monostearate	1.0
(4)	stearic acid	0.5
(5)	behenyl alcohol	0.5
(6)	squalane	8.0
(7)	preservative	suitable amount
(8)	Coccinia grandis Voight extract *1	0.1
(9)	Mammea siamensis Kosterm. extract *1	0.1
(10)	Michelia champaca L. extract *1	0.1
(11)	carboxyvinyl polymer	0.1
(12)	sodium hydroxide	0.05
(13)	ethyl alcohol	5.0
(14)	purified water	balance
(15)	fragrance	suitable amount

*1 Produced in Working Example 9

Production

A. Ingredients (11) to (14) are heated to combine and kept at 70°C.

B. Ingredients (1) to (7) are heated to combine and kept at 70°C.

C. A is added to B and evenly emulsified.

D. C is cooled, then ingredients (8) to (10) and (15) are added and evenly combined to give an emulsion.

Working Example 13

Cream: A cream was prepared by the following formula using the production method described below.

	Formula	(%)
(1)	polyoxyethylene (40E.O) sorbitan monolaurate	2.0
(2)	glycerin monostearate (self-emulsifying)	5.0
(3)	stearic acid	5.0
(4)	behenyl alcohol	0.5
(5)	squalane	15.0
(6)	cetyl isooctoate	5.0
(7)	preservative	suitable amount
(8)	1,3-butylene glycol	5.0
(9)	Gloriosa superba L. extract *1	1.0
(10)	Micromelum minutum Seem. extract *1	1.0
(11)	Orthosiphon stamineus extract *1	1.0
(12)	purified water	balance
(13)	fragrance	suitable amount

*1 Produced in Working Example 9 /15

Production

A. Ingredients (1) to (7) are heated to 70°C and dissolved.

B. Ingredients (8) and some of (12) are heated to 70°C.

C. B is added to A, then ingredients (9) to (11), the rest of (12), and (13) are added while cooling to give a cream.

The toilet water of Working Example 11, the emulsion of Working Example 12, and the cream of Working Example 13 all had excellent stability over time, prevented inflammation and darkening of the skin due to peroxide lipids by application to the skin, and produced beautiful skin with good tone and luster. Moreover, no skin conditions were observed that were problematical in terms of safety, such as itching or rash.

Working Example 14

Pack: A pack was prepared by the following formula using the production method described below.

Formula	(%)
(1) polyvinyl alcohol	20.0
(2) ethyl alcohol	20.0
(3) glycerin	5.0
(4) kaolin	6.0
(5) Hibiscus sabdariffa L. extract *1	5.0
(6) preservative	suitable amount
(7) fragrance	suitable amount
(8) purified water	balance

*1 Produced in Working Example 9

Production

A. Ingredients (1), (3), (4), and (8) are combined, heated to 70°C, and agitated.

B. Ingredients (2) and (6) are combined.

C. The above B is added to the previous A and combined, then cooled, and ingredients (5) and (7) are evenly dispersed to give a pack.

The pack of Working Example 14 had excellent stability over time, could inhibit inflammation of the skin and prevent skin "darkness" by repeated application to the skin, and produced beautiful, clear skin. Moreover, no skin conditions were observed that were problematical in terms of safety, such as itching or rash.

Working Example 15

Liquid Foundation: A liquid foundation was prepared by the following formula using the production method described below.

Formula	(%)
(1) lanolin	7.0
(2) fluid paraffin	5.0
(3) stearic acid	2.0
(4) hexadecanol	1.0
(5) glycerin	5.0
(6) triethanolamine	1.0
(7) carboxymethylcellulose	0.7
(8) purified water	balance
(9) mica	15.0
(10) talc	6.0
(11) coloring pigment	6.0
(12) Morinda citrifolia L. extract *1	0.5
(13) Mitragyna speciose (Korth.) Havil. extract *1	1.0
(14) fragrance	suitable amount

*1 Produced in Working Example 9 /16

Production

A. Ingredients (1) to (4) are combined and dissolved.

B. Ingredients (9) to (11) are added to A and evenly combined.

C. Ingredients (5) to (8) are evenly dissolved and kept at 70°C.

D. C is added to B and evenly emulsified.

E. D is cooled, then ingredients (12) to (14) are added to give a liquid foundation.

The liquid foundation of Working Example 15 had excellent stability over time, and prevented skin inflammation and darkening by application to the skin. Moreover, no skin conditions were observed that were problematical in terms of safety, such as itching or rash.

Working Example 16

Gel Ointment: A gel ointment was prepared by the following formula using the production method described below.

	Formula	(%)
(1)	carboxyvinyl polymer	1.0
(2)	triethanolamine	1.0
(3)	ethyl alcohol	20.0
(4)	Solanum trilosatum L. extract *1	5.0
(5)	Mesua ferrea L. extract *1	5.0
(6)	purified water	balance

*1 Produced in Working Example 9

Production

A. Ingredients (1) and (3) to (6) are combined and dissolved.

B. Ingredient (2) is added to A and evenly combined to give a gel ointment.

The gel ointment of Working Example 16 had excellent stability over time, prevented inflammation and darkening of the skin due to peroxide lipids by application to the skin, and produced beautiful skin with good tone and luster. Moreover, no skin conditions were observed that were problematical in terms of safety, such as itching or rash.

Working Example 17

Production of Plant Extract (Antimicrobial Agent): 100 mL Ethyl alcohol of 50% (v/v) moisture concentration were added to 10 g of each plant, dry, listed in Table 9 and extracted for three days at room temperature, then filtered to give each plant extract. This was taken as the antimicrobial agent of the present invention. The dry solid parts of these extracts are also given in Table 9.

[Table 9] /17

Antimicrobial Agent		Dry Solid Parts (%)
Invention Product	Artocarpus lakoocha Roxb. extract *1	4.1
	Streblus asper Lour. extract *1	1.2
	Blumea balsamifera DC. extract *1	2.0
	Pluchea indica (L.) Less. extract *1	3.4
	Coccinia indica Wight & Arnott extract *1	1.8
	Coccinia grandis Voight extract *1	1.8
	Gloriosa superba L. extract *1	2.2
	Heliotropium indicum R. Br. extract *1	2.7
	Hibiscus sabdariffa L. extract *1	3.7
	Mammea siamensis Kosterm. extract *1	2.3
	Michelia champaca L. extract *1	3.3
	Micromelum minutum Seem. extract *1	1.4
	Murraya paniculata Jack extract *1	2.8
	Mitragyna speciose (Korth.) Havil. extract *1	2.3
	Morinda citrifolia L. extract *1	4.8
	Randia siamensis Craib. extract *1	2.1
	Orthosiphon stamineus extract *1	0.8
	Solanum trilosatum L. extract *1	2.9
	Solanum violaceum Ortega extract *1	1.2
Comparison Products	Morus bombycis extract *2	1.8
	Glycyrrhiza glabra extract *2	2.0
	aloe extract *2	1.9

*1 Produced in Working Example 17
*2 Produced in Reference Example 2

Reference Example 2

Production of Morus bombycis Extract, Glycyrrhiza glabra Extract, and Aloe Extract: 10 mL Ethyl alcohol of 50% (v/v) moisture concentration were added to 10 g each of Morus bombycis (Pharmacopoeia Japonica), Glycyrrhiza glabra (Pharmacopoeia Japonica), and aloe (Pharmacopoeia Japonica) and extracted for three days at room temperature, then filtered to give Morus bombycis extract, Glycyrrhiza glabra extract, and aloe extract. The dry solid

parts of these extracts are also given in Table 9.

Test Example 5

Test of Antimicrobial Effect: Antimicrobial effect was investigated for the antimicrobial agents of the present invention and the Morus bombycis extract, Glycyrrhiza glabra extract, and aloe extract obtained in Reference Example 2, which are already known to have an antimicrobial effect. Specifically, first, dry solids of each extract were diluted to 1% solutions by ethyl alcohol of 50% (v/v) moisture concentration, and 10 mL of each solution were distributed into dry-sterilized test tubes.

Next, 10^5 to 10^6 cfu/mL Escherichia coli (E. c), Pseudomonas aeruginosa (Ps. a), Staphylococcus aureus (St. a), Candida albicans (C. a), and Aspergillus niger (A. n) were inoculated in the test tubes (one strain per test tube) and cultured at 25°C for seven days, and the biomass was measured after 24 hours and after seven days. The results are given in Tables 10 through 31.

[Table 10]

Invention Antimicrobial Agent: Artocarpus lakoocha Roxb. Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	3.0×10^3	< 10
Ps. a	3.0×10^5	1.0×10^2	< 10
St. a	4.8×10^5	9.0×10^3	< 10
C. a	4.5×10^5	6.0×10^3	< 10
A. n	5.5×10^5	2.0×10^4	< 10

[Table 11] /18

Invention Antimicrobial Agent: Streblus asper Lour. Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	2.0×10^2	< 10
Ps. a	3.0×10^5	1.5 x 10	< 10
St. a	4.8×10^5	6.3×10^3	< 10
C. a	4.5×10^5	< 10	< 10
A. n	5.5×10^5	4.0×10^3	< 10

[Table 12]

Invention Antimicrobial Agent: Blumea balsamifera DC. Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	7.2 x 10	< 10
Ps. a	3.0×10^5	8.5×10^2	< 10
St. a	4.8×10^5	4.6 x 10	< 10
C. a	4.5×10^5	5.0 x 10	< 10
A. n	5.5×10^5	2.0×10^3	< 10

[Table 13]

Invention Antimicrobial Agent: Pluchea indica (L.) Less. Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	3.0×10^3	< 10
Ps. a	3.0×10^5	6.5×10^2	< 10
St. a	4.8×10^5	< 10	< 10
C. a	4.5×10^5	< 10	< 10
A. n	5.5×10^5	2.9×10^3	< 10

[Table 14] /19

Invention Antimicrobial Agent: Coccinia indica Wight & Arnott Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	6.4×10^3	< 10
Ps. a	3.0×10^5	5.1×10^2	< 10
St. a	4.8×10^5	2.6×10	< 10
C. a	4.5×10^5	8.0×10^2	< 10
A. n	5.5×10^5	4.0×10^2	< 10

[Table 15]

Invention Antimicrobial Agent: Coccinia grandis Voight Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	< 10	< 10
Ps. a	3.0×10^5	< 10	< 10
St. a	4.8×10^5	3.0×10^3	< 10
C. a	4.5×10^5	5.6×10^4	< 10
A. n	5.5×10^5	3.1×10^5	< 10

[Table 16]

Invention Antimicrobial Agent: Gloriosa superba L. Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	2.1×10	< 10
Ps. a	3.0×10^5	6.3×10^2	< 10
St. a	4.8×10^5	5.0×10	< 10
C. a	4.5×10^5	3.0×10^2	< 10
A. n	5.5×10^5	5.1×10^2	< 10

[Table 17]

Invention Antimicrobial Agent: Heliotropium indicum R. Br. Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	< 10	< 10
Ps. a	3.0×10^5	< 10	< 10
St. a	4.8×10^5	< 10	< 10
C. a	4.5×10^5	< 10	< 10
A. n	5.5×10^5	< 10	< 10

/20

[Table 18]

Invention Antimicrobial Agent: Hibiscus sabdariffa L. Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	4.5×10^2	< 10
Ps. a	3.0×10^5	3.6×10^2	< 10
St. a	4.8×10^5	8.0×10^2	< 10
C. a	4.5×10^5	5.0×10^2	< 10
A. n	5.5×10^5	6.0×10^2	< 10

[Table 19]

Invention Antimicrobial Agent: Mammea siamensis Kosterm. Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	< 10	< 10
Ps. a	3.0×10^5	< 10	< 10
St. a	4.8×10^5	1.0 x 10	< 10
C. a	4.5×10^5	< 10	< 10
A. n	5.5×10^5	2.0×10^2	< 10

[Table 20]

Invention Antimicrobial Agent: Michelia champaca L. Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	5.0×10	< 10
Ps. a	3.0×10^5	3.1×10^2	< 10
St. a	4.8×10^5	4.0×10^2	< 10
C. a	4.5×10^5	6.0×10^3	< 10
A. n	5.5×10^5	5.0×10^2	< 10

[Table 21] /21

Invention Antimicrobial Agent: Micromelum minutum Seem. Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	2.5×10^3	< 10
Ps. a	3.0×10^5	3.0×10^3	< 10
St. a	4.8×10^5	5.0×10^3	< 10
C. a	4.5×10^5	2.0×10^3	< 10
A. n	5.5×10^5	1.0×10^3	< 10

[Table 22]

Invention Antimicrobial Agent: Murraya paniculata Jack Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	8.0×10^2	< 10
Ps. a	3.0×10^5	9.5×10	< 10
St. a	4.8×10^5	7.5×10^2	< 10
C. a	4.5×10^5	6.0×10^3	< 10
A. n	5.5×10^5	5.0×10^2	< 10

[Table 23]

Invention Antimicrobial Agent: Mitragyna speciose (Korth.) Havil. Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	< 10	< 10
Ps. a	3.0×10^5	< 10	< 10
St. a	4.8×10^5	< 10	< 10
C. a	4.5×10^5	< 10	< 10
A. n	5.5×10^5	5.0×10^2	< 10

[Table 24]

Invention Antimicrobial Agent: Morinda citrifolia L. Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	6.5×10	< 10
Ps. a	3.0×10^5	3.5×10	< 10
St. a	4.8×10^5	2.5×10	< 10
C. a	4.5×10^5	5.5×10	< 10
A. n	5.5×10^5	5.5×10^2	< 10

[Table 25] /22

Invention Antimicrobial Agent: Randia siamensis Craib. Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	7.0×10^3	< 10
Ps. a	3.0×10^5	4.0×10^2	< 10
St. a	4.8×10^5	3.5×10	< 10
C. a	4.5×10^5	2.1×10^2	< 10
A. n	5.5×10^5	6.0×10^2	< 10

[Table 26]

Invention Antimicrobial Agent: Orthosiphon stamineus Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	7.0×10^2	< 10
Ps. a	3.0×10^5	4.0×10^2	< 10
St. a	4.8×10^5	3.5×10^2	< 10
C. a	4.5×10^5	2.1×10^2	< 10
A. n	5.5×10^5	6.0×10^2	< 10

[Table 27]

Invention Antimicrobial Agent: Solanum trilosatum L. Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	1.0×10^3	< 10
Ps. a	3.0×10^5	2.5×10^2	< 10
St. a	4.8×10^5	4.0×10^2	< 10
C. a	4.5×10^5	1.0×10^2	< 10
A. n	5.5×10^5	3.5×10^2	< 10

[Table 28] /23

Invention Antimicrobial Agent: Solanum violaceum Ortega Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	5.0×10	< 10
Ps. a	3.0×10^5	< 10	< 10
St. a	4.8×10^5	< 10	< 10
C. a	4.5×10^5	4.0×10^3	< 10
A. n	5.5×10^5	2.5×10^3	< 10

[Table 29]

Comparison Product: Morus bombycis Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	8.0×10^3	2.6×10^7
Ps. a	3.0×10^5	4.2×10^4	1.8×10^8
St. a	4.8×10^5	6.7×10^4	3.5×10^8
C. a	4.5×10^5	2.0×10^6	9.5×10^6
A. n	5.5×10^5	1.0×10^3	3.8×10^6

[Table 30]

Comparison Product: Glycyrrhiza glabra Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	3.4×10^3	2.1×10^6
Ps. a	3.0×10^5	5.6×10^2	3.4×10^5
St. a	4.8×10^5	8.1×10^3	5.2×10^6
C. a	4.5×10^5	5.5×10^4	5.4×10^6
A. n	5.5×10^5	6.0×10^5	4.9×10^5

[Table 31]

Comparison Product: Aloe Extract			
	Biomass (cfu/mL)		
Strain	When Inoculated	After 24 Hours	After 7 Days
E. c	5.0×10^5	8.1×10^2	3.1×10^6
Ps. a	3.0×10^5	6.2×10^3	2.6×10^6
St. a	4.8×10^5	5.4×10^2	5.5×10^6
C. a	4.5×10^5	5.8×10^2	5.8×10^6
A. n	5.5×10^5	6.8×10^5	5.1×10^5

As is clear from the results in Tables 10 through 31, the /24 antimicrobial agents of the present invention showed higher antimicrobial effect against microorganisms such as bacteria and fungi than conventional Morus bombycis extract, Glycyrrhiza glabra

extract, and aloe extract.

Test Example 6

Patch Test: A patch test was conducted for the purpose of confirming the safety of the antimicrobial agents of the present invention. Specifically, each of the antimicrobial agents obtained in Working Example 17 was coated on a patch (Fintenbar [as transliterated], manufactured by Taisho Pharmaceutical Co., Ltd.), which was affixed on the inside of the upper arm of thirty subjects and sealed for 24 hours, then checked for the presence or absence of skin irritation after thirty minutes and again after 24 hours.

As a result, no skin irritation was found at either time of thirty minutes or 24 hours after removing the patches 24 hours after affixing to thirty subjects. Therefore, it was confirmed that the antimicrobial agent of the present invention has very high safety.

Working Example 18

Antimicrobial Agent: The following formula was combined to prepare an antimicrobial agent.

	Formula	(%)
(1)	Mitragyna speciose (Korth.) Havil. extract *1	50.0
(2)	glycerin	25.0
(3)	purified water	25.0

*1 Produced in Working Example 17

The antimicrobial agent of Working Example 18 was tested for antimicrobial effect in the same way as in Test Example 5. As a result, absolutely no bacterial growth was found.

Working Example 19

Mouthwash: The following formula was combined to prepare a mouthwash.

Formula		(%)
(1)	Solanum violaceum Ortega extract *1	20.0
(2)	cetyl pyridinium hydrochloride	0.2
(3)	Pluronic	1.0
(4)	fragrance	suitable amount
(5)	purified water	balance

*1 Produced in Working Example 17

The antimicrobial agent of Working Example 19 was tested for antimicrobial effect in the same way as in Test Example 5. As a result, absolutely no bacterial growth was found.

Working Example 20

Toilet Water: A toilet water was prepared by the following formula using the production method described below.

Formula		(%)
(1)	glycerin	5.0
(2)	1,3-butylene glycol	6.5
(3)	polyoxyethylene (20E.O) sorbitan monolaurate	1.2
(4)	ethyl alcohol	5.0
(5)	Heliotropium indicum R. Br. extract *1	10.0
(6)	Solanum trilosatum L. extract *1	10.0
(7)	Morus bombycis extract *2	0.1
(7)	preservative	suitable amount
(8)	fragrance	suitable amount
(9)	purified water	balance

*1 Produced in Working Example 17
*2 Produced in Reference Example 2

Production

A. Ingredients (3), (4), and (8) are combined and dissolved.

B. Ingredients (1), (2), (5), (6), (7), and (9) are combined and dissolved.

C. A and B are evenly combined to give a toilet water.

Working Example 21

Emulsion: An emulsion was prepared by the following formula using the production method described below.

	Formula	(%)
(1)	polyoxyethylene (10E.O) sorbitan monolaurate	1.0
(2)	polyoxyethylene (60E.O) sorbitan monolaurate	0.5
(3)	glyceryl monostearate	1.0
(4)	stearic acid	0.5
(5)	behenyl alcohol	0.5
(6)	squalane	8.0
(7)	2-ethyl hexyl paramethoxycinnamate	1.0
(8)	Solanum violaceum Ortega extract *1	20.0
(9)	polyethylene glycol	0.5
(10)	carboxyvinyl polymer	0.1
(11)	sodium hydroxide	0.05
(12)	ethyl alcohol	5.0
(13)	purified water	balance
(14)	fragrance	suitable amount

*1 Produced in Working Example 17 /25

Production

A. Ingredients (9) to (13) are heated to combine and kept at 70°C.

B. Ingredients (1) to (7) are heated to combine and kept at 70°C.

C. A is added to B and evenly emulsified.

D. C is cooled, then ingredients (8) and (14) are added and evenly combined to give an emulsion.

Working Example 22

Cream: A cream was prepared by the following formula using the production method described below.

	Formula	(%)
(1)	polyoxyethylene (40E.O) sorbitan monolaurate	2.0
(2)	glycerin monostearate (self-emulsifying)	5.0
(3)	stearic acid	5.0
(4)	behenyl alcohol	0.5
(5)	squalane	15.0
(6)	cetyl isooctoate	5.0
(7)	tocopherol acetate	0.1
(8)	methyl paraffin	0.1
(9)	glycerin	2.0
(10)	1,3-butylene glycol	5.0
(11)	Mammea siamensis Kosterm. extract *1	1.0
(12)	Murraya paniculata Jack extract *1	1.0
(13)	dipotassium glycyl ricinoleate	0.1
(14)	purified water	balance
(15)	fragrance	suitable amount

*1 Produced in Working Example 17

Production

A. Ingredients (1) to (7) are heated to 70°C and dissolved.

B. Ingredients (8) to (10) and some of (14) are heated to 70°C.

C. B is added to A, then ingredients (11), (12), (13), the rest of (14), and (15) are added while cooling to give a cream.

The toilet water of Working Example 20, the emulsion of Working Example 21, and the cream of Working Example 22 all showed no bacterial growth, had excellent stability over time, caused no irritation even after prolonged application to the skin, and produced beautiful, clear skin.

Working Example 23

Pack: A pack was prepared by the following formula using the production method described below.

Formula	(%)
(1) polyvinyl alcohol	20.0
(2) ethyl alcohol	20.0
(3) glycerin	5.0
(4) kaolin	6.0
(5) Streblus asper Lour. extract *1	5.0
(6) Hibiscus sabdariffa L. extract *1	5.0
(7) 1-menthol	0.2
(8) fragrance	0.1
(9) purified water	balance

*1 Produced in Working Example 17 /26

Production

A. Ingredients (1), (3), (4), and (9) are combined, heated to 70°C, and agitated.

B. Ingredients (2) and (6) are combined.

C. The above B is added to the previous A and combined, then cooled, and (5), (6), and (8) are evenly dispersed to give a pack.

The pack of Working Example 23 showed no bacterial growth, had excellent stability over time, caused no irritation even after prolonged application to the skin, and produced beautiful, well-toned skin.

Working Example 24

Liquid Foundation: A liquid foundation was prepared by the following formula using the production method described below.

Formula	(%)
(1) lanolin	7.0
(2) fluid paraffin	5.0
(3) stearic acid	2.0
(4) hexadecanol	1.0
(5) glycerin	5.0
(6) triethanolamine	1.0
(7) carboxymethylcellulose	0.7
(8) purified water	balance
(9) mica	15.0
(10) talc	6.0
(11) titanium oxide	3.0
(12) coloring pigment	6.0
(13) Blumea balsamifera DC. extract *1	0.5
(14) oxybenzone	0.1
(15) fragrance	suitable amount

*1 Produced in Working Example 17

Production

A. Ingredients (1) to (4) and (14) are combined and dissolved.

B. Ingredients (9) to (12) are added to A and evenly combined.

C. Ingredients (5) to (8) are evenly dissolved and kept at 70°C.

D. C is added to B and evenly emulsified.

E. D is cooled, then ingredients (13) and (15) are added to give a liquid foundation.

Working Example 25

Emulsion for Sunscreen: An emulsion for sunscreen was prepared by the following formula using the production method described below.

	Formula	(%)
(1)	stearic acid	2.0
(2)	methanol	1.0
(3)	polyoxyethylene sorbitan monolaurate (20E.O)	0.5
(4)	sorbitan sesquioleate	0.5
(5)	2-ethyl hexyl paramethoxycinnamate	8.0
(6)	cetyl 2-ethylhexanoate	12.0
(7)	1,3-butylene glycol	10.0
(8)	carboxyvinyl polymer	0.2
(9)	triethanolamine	0.5
(10)	Orthosiphon stamineus extract *1	2.0
(11)	Artocarpus lakoocha Roxb. extract *1	2.0
(12)	disodium ethylenediaminetetraacetate	0.1
(13)	purified water	balance
(14)	L-ascorbyl magnesium phosphate	0.1
(15)	titanium oxide	3.0
(16)	fragrance	suitable amount

*1 Produced in Working Example 17 /27

Production

A. Ingredients (1) to (6) and (15) are heated to combine and kept at 75°C.

B. Ingredients (7) to (9) and (12) to (14) are heated to combine and kept at 75°C.

C. B is gradually added to A.

D. Ingredients (10), (11), and (16) are added while cooling to give an emulsion for sunscreen.

The liquid foundation of Working Example 24 and the emulsion for sunscreen of Working Example 25 both showed no bacterial growth, had excellent stability over time, caused no irritation even after prolonged application to the skin, and prevented darkening and spots due to sun exposure or the like.

Working Example 26

Hair Tonic: A hair tonic was prepared by the following formula using the production method described below.

	Formula	(%)
(1)	Morinda citrifolia L. extract *1	0.1
(2)	Coccinia indica Wight & Arnott extract *1	0.1
(3)	Coccinia grandis Voight extract *1	0.1
(4)	isopropyl methyl phenol	0.1
(5)	menthol	0.1
(6)	ethyl alcohol	40.0
(7)	fragrance	suitable amount
(8)	purified water	balance

*1 Produced in Working Example 17

Production

A. Ingredients (4) to (7) are combined and dissolved.

B. Ingredients (1), (2), (3), and (8) are combined and dissolved.

C. A is added to B and evenly combined to give a hair tonic.

The hair tonic of Working Example 26 showed no bacterial growth, had excellent stability over time, caused no irritation even after prolonged application to the skin, and prevented dandruff and itching.

[Effects of the Invention]

As explained above, the skin whitening agent and agent for external use containing this of the present invention have inhibitory effects on melanin production and tyrosine activity, achieve a high inhibitory effect on pigment deposits, and are effective for preventing and improving skin darkening, spots, and freckles resulting from sun exposure or the like.

The active oxygen scavenging agent and agent for external use containing this of the present invention have excellent active oxygen scavenging effect ——specifically, extremely high effect in correcting and preventing production of peroxide lipids caused by production of active oxygen between skin surfaces and within skin, and inflammation, darkening, and aging of skin——, have excellent safety on skin, and are extremely useful in cosmetic and clinical settings.

Furthermore, the antimicrobial agent and agent for external use containing this of the present invention are safe and have excellent antimicrobial effect, and agents for external use containing these, such as cosmetics or pharmaceutical products, show no growth of microorganisms such as bacteria, have excellent antimicrobial effect, and are effective for preventing and improving skin problems caused by microorganisms.